Knowledge Acquisition Session Report
NCI – DCP Protocol Information Office

Session Date: June 27, 2000 **Session Time:** 2:00 – 4:00 P.M. EST

Session Topic: PIO Information Processes and Procedures

Knowledge Analysts: Lisa Chatterjee, Oracle; Bill McCurry, Robert Harding, ScenPro, Inc.

Organization: Protocol Information Office, NCI Division of Cancer Prevention

Session Location: Teleconference: CCS: Mt. View, CA; DCP: Rockville, Maryland; ScenPro, Inc.: Richardson, TX

Type of Session:

X Interview _____ Task Analysis _____ Scenario Analysis
_____ Concept Analysis _____ Observation _____ Structured Interview
_____ Other:

Documentation: KA Session Report
Items received from CCS through DCP-PIO

- NCI, DCP. Cancer Chemoprevention Clinical Trials Quality Assurance Audits and Safety Data Reporting. NCI Contract NO2-CN-75009. April 17-18, 2000. Maria Shabe: QA/QC Associate. *[Discusses monitoring vs. auditing]*
- NCI, DCP. Cancer Chemoprevention Clinical Trials Monitoring and Coordination Support. NCI Contract NO2-CN-75009. April 17-18, 2000. Donya Bagheri, MS, DABT Director, Drug Development. *[Defines monitoring contract tasks, Types of monitoring, Decision making for selecting monitoring method]*
- Routine Monitoring Visit Report *[CCS report to DCP following monitoring visit]*
- Study Monitoring, Qualification Visit, Initiation Visit, Routine Monitoring Visit, Closeout Visit. *[Definitions. Components of each type of monitoring visit]*
- Cumulative Listing of Adverse Events by Dose within Protocol, by Body System; Current Listing of Dropouts by Dose within Protocol, Cumulative Listing of Deaths by Dose within Protocol Agent: 9-cis-Retinoic Acid.
- Clinical Trial of Difluoromethylornithine (DFMO) in Oral Dysplastic Leukoplakia. Table 4: Events of Possible Side Events. Adverse Events Report – Aug 31, 1999 UT MD Anderson Cancer Center
- Format for Protocol Review Report (attachment D) [*To be included in CCS' quarterly progress report to DCP]*
- Format for NCI Study Updates (attachment C) *[Example of new format for the bi-weekly CCS conference call.]*
- On-Site Data Monitoring Form for the Quarterly Report (attachment E) *[Format requested by DCP for CCS to report (quarterly) the result of site visits]*

Documentation (continued):

- Sections of an Initial IND

- Track and Coordinate IND Applications, Regulatory Databases *[Information about CCS databases]*
- Chemopreventive Agent Support
- Master List of Chemopreventive Agents (MLCHEM)
- Master List Animal Efficacy Scheme
- Master List of Chemopreventive Agents: Sample Report of Animal Efficacy Database
- Chemopreventive Drug Development: Class Studies
- Class Study Approach to Identification and Development of Chemopreventive Agents
- CCS Associates, Inc. Organizational Chart
- IND Submission Tracking Report – DFMO (page 1 of 19)
- Requirements for FINAL REPORT: Phase I & II Clinical Trials of Chemoprevention Agents, Instructions and Templates *[Format for MAH final report]*
- NCI, Division of Cancer Prevention Serious Adverse Event Form

General Topic Area

Clinical Chemopreventive Study Associates' databases and involvement in DCP Clinical Research

Session Goal

Document CCS processes and databases used to support DCP Clinical Research

Report Summary

CCS (Clinical Chemopreventive Study Associates) participates in almost every aspect of DCP (Division of Cancer Prevention) clinical research, and records related information in multiple databases. CCS tracks review, patient accrual information, required documents, organizations and investigators. CCS personnel perform regulatory and monitoring functions for DCP studies and manage the pre-FDA (Food and Drug Administration) protocol review process. CCS maintains over a dozen linked databases.

Agents

Chemopreventive Clinical Services (CCS) maintains a master list of all agents used in pre-clinical and clinical cancer prevention trials. The CCS database Chemoprevention Chemicals (CPCHEM) contains this master list.

A CCS chemist assigns the master name, which is used for database indexing. The chemist searches online databases to determine the appropriate name to assign each agent. The chemist then records the agent name in capital letters and assigns a unique registry number to each name.

CCS staff, including CCS president Caroline Sigmund, review the master name before it is entered in CPCHEM. Once an agent is entered in CPCHEM, CCS personnel can search for it by registry number, by chemical name, and by agent synonyms.

CPCHEM is a diverse database that contains:

- Biological and chemical categories database
- Chemical structures database
- Animal Efficacy database
- Intermediate endpoint database
- Short-term test results database
- Related activities database
- Human studies database
- Combination agents databases (animal efficacy, intermediate endpoint, short-term test results, and human studies combination databases)
- Chemoprevention literature collection and database

Organizations and Investigators

Chemopreventive Clinical Services (CCS) tracks organizations and investigators in two databases. They are the pre-clinical administrative database CTCONTR and the clinical administrative database CTCLCON. CTCONTR (pre-clinical) contains roughly 300 records on organizations, and CTCLCON (clinical) contains roughly 1200 records on investigators.

Both databases are linked to a regulatory database called Principal Investigator Track (PITRACK). The key fields providing these links are contract number, protocol number (a local number assigned by the IRB), and agent identification. PITRACK contains information on how principal investigators link to subordinate investigators. Figure 1 shows the CCS organization and investigator information databases that are linked to CCS' regulatory database PITS.

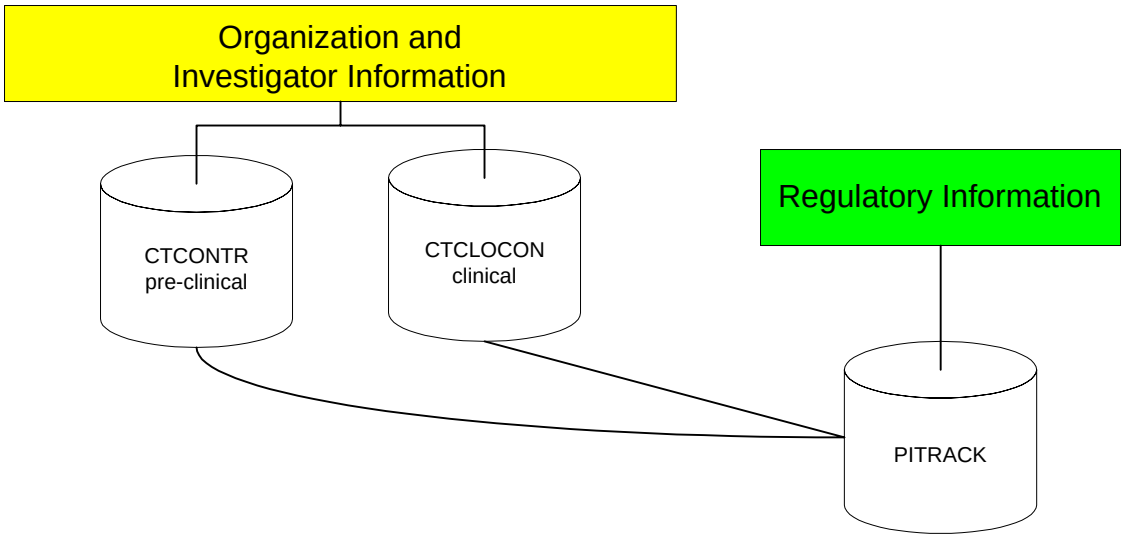

Figure 1: Links Between CCS' Organization, Investigator and Regulatory Databases

Reporting: Patient Accrual

Chemopreventive Clinical Services (CCS) tracks patient accrual for most cancer prevention studies and records it in a database called Protocol Information Tracking System (PITS). PITS contains other administrative information on protocols used to facilitate the protocol review process. It contains information on:

- Reports due
- Forecasted accruals
- Planned accrual rate
- Planned accrual period
- Actual accruals.

The PITS database also generates the Medical Monitor meeting minutes.

Accrual information is provided by quarterly reports, semi-annual reports, annual reports, draft final reports, final reports and site visit reports. CCS uses funding type to track accrual. Table 1 shows the type of funding associated with each report.

Contracts	Grants
Quarterly Reports	Semi-Annual Reports
Both Contracts and Grants	
Annual Reports Draft Final Reports Final Reports Site Visit Reports	

Table 1: Reports Containing Accrual Information by Funding Type

CCS' Chemoprevention Clinical database (CPCLIN) provides an overview of patient accrual information.

Monitoring: Site Visits

Chemopreventive Clinical Services (CCS) uses the clinical administrative database CPCLCON to schedule annual site visits. CCS staff logs the date of the last site visit in CPCLCON, which then assigns a tentative date for the next visit. Site Visit Reports are due ten days after the site visit. Also, CCS schedules site visits whenever a Medical Monitor requests it.

CCS use a standard Site Visit Report form. All information on the form is abstracted into either CPCLIN (containing overview information) or CLINSUM (containing detailed text fields). CLINSUM includes:

- Summary of the protocol
- Results of safety and lab endpoints
- Summary of accrual
- Summary of the monitoring visit

Adverse Event and Serious Adverse Event Tracking

Designers of cancer prevention trials usually do not anticipate many adverse events (AE) and serious adverse events (SAE) because the study participants are essentially healthy people. Parties responsible for the conduct of prevention trials take each adverse event very seriously. CCS Clinical Research Associates (CRA) endeavor to gather the most complete information possible on each adverse event.

Chemopreventive Clinical Services (CCS) personnel record serious adverse events and in their Adverse Event tracking database (AETRACK). CCS tracks non-Investigational New Drug (IND) study adverse events as well as AEs associated with INDs. AETRACK has a field recording the fact that the principal investigator submitted it as an SAE.

The CCS regulatory group, Clinical Research Associates, Medical Monitors, and in some cases the Principal Investigator and/or the pharmaceutical company collaborate to evaluate SAEs. The group uses ICH requirements, and Common Toxicity Criteria to help determine if an adverse event is serious.

CCS immediately informs Medical Monitors, the FDA, and the DCP Protocol Information Office after the AE is determined to be serious. If CCS determines it is not serious, the event will remain as an AE with a field showing that it was submitted as a SAE.

Common Toxicity Criteria

Common Toxicity Criteria (CTC) are used in all DCP studies handled by CCS. Toxicity criteria defined in a protocol usually cover specific study situations where the CTC do not apply. A table in the progress report allows Medical Monitors to fill in toxicity information based on Common Toxicity Criteria. AETRACK contains some CTC grading.

Investigational New Drug

Chemopreventive Clinical Services (CCS) takes an active role in the cancer prevention Investigational New Drug (IND) process. CCS stays abreast of upcoming IND Protocols and INDs in a variety of ways:

- Work statements
- Medical Monitor meetings held every other week
- Clinical development plans
- Through general awareness of companies that have clinical trial agreements with the Division of Cancer Prevention (DCP).

CCS' Regulatory database tracks IND information. The database includes:

- AMTRACK (Amendment Tracking)
- INDTRACK (IND Tracking)
- PITRACK (Protocol Information Tracking)

CCS tracks and maintains archives of all IND submissions in a database called SAFTRACK. In cases where a Principal Investigator (PI) owns the IND, CCS only records the fact of that ownership. In these cases, the PI is responsible for all IND reporting.

Protocols

CCS annually reports the status of all open protocols for each IND. CCS ensures that a protocol has all the necessary components needed for its attachment to an IND. A protocol review template aids CCS personnel in this task. The review template contains a section that asks for IND elements.

IND Submission

The Food and Drug Administration (FDA) has specific regulations for the contents of an IND. The initial IND documentation sent to the FDA includes:

- Summary
- Rationale
- Protocol
- Investigators section
- Agent Chemistry and Manufacturing
- Pharmacology and Toxicology of the Drug (including both pre-clinical and clinical information)

- Investigator brochure

Ongoing IND submissions include:

- Protocol amendments
- Pharmacology updates
- Annual reports
- SAE Reports
- Answers to FDA queries

Occasionally, an IND will be assembled, but cannot be submitted until a protocol to be attached. In other cases, the protocol is ready, but the IND needs to be composed. Once the IND is completed, CCS adds it to their IND tracking database.

IND Tracking

CCS tracks all IND submission in INDTRACK. During the life of an IND, each submission to the FDA is given a sequence number as an identifier. The original submission may be given "000", the next "001", and so on. CCS made 38 IND submissions to the FDA between January 1 and June 30, 2000.

Once the FDA central documents room receives the IND, they assign a number and determine which FDA division will handle the IND. Recently INDs from both DCP and CTEP have been sent to divisions other than Oncology. CCS is now working with INDs in four or five different FDA divisions. Some FDA divisions use a paper-based system to track INDs. CCS tracks the location of an IND as it progresses through the FDA in INDTRACK. CCS also tracks 1572s for IND protocols.

Regulatory Issues

Food and Drug Administration Form 1572

Lead investigators attest that they are overseeing all activity at each site and for each study by signing Food and Drug Administration (FDA) Form 1572 (Statement of Investigator). The form is a legal document listing all sub-investigators at that site, all clinical labs, and all nurse practitioners. CCS obtains an FDA Form 1572 from lead investigators for each site and study they are working on. Lead investigators must re-submit 1572s annually.

Chemopreventive Clinical Services (CCS) monitors each site to evaluate whether the investigator can adequately oversee the activity. If an investigator can't reasonably oversee a site's activity on a regular basis, a new PI for that site with a form 1572 will be found. CCS personnel use Form 1572 as one way of identifying labs being used in a protocol. This assists CCS in collecting information needed for lab certification. CCS documents Form 1572 data in PITRACK.

Investigational Review Board Approvals

FDA regulators request Investigational Review Board (IRB) information when performing site visits. Clinical Research Associates (CRA) communicate frequently with the sites and ensure that they report IRB approval information. CCS tracks IRB approval and expiration dates in AMTRACK.

Assurances

CCS ensures all NCI studies are covered either by a Multiple Project Assurance (MPA) or a Single Project Assurance (SPA). Medical Monitors work with CCS regulatory personnel to negotiate the assurances. CCS uses a website to review assurance information and to track the progress/ status of each assurance. CCS Regulatory Affairs Specialist Margaret R. Scheitrum keeps abreast of OPRR developments by attending workshops. Further KA is needed to identify which CCS database records MPA and SPA data.

Review

The Food and Drug Administration (FDA) requires 30 days for protocol review. Each subsequent protocol filed for an IND requires another 30 days for review. The FDA may also require response to comments, but there is no time limit on those responses, and they would not delay the IND approval.

Pre-FDA Protocol Review

When the original protocol is submitted, Chemopreventive Clinical Services (CCS) performs the following types of reviews:

- Clinical Research Associate (CRA)
- Agent Expert
- Statistical
- Scientific
- Regulatory
- Nutrition
- Management

These reviews are completed in ten business days, and comments are sent to the Protocol Information Office (PIO). PIO personnel use the comments as a reference during subsequent review board meetings. Additional comments may arise from those DCP reviews, and the results are sent back to the Principal Investigator (PI). The PI has four to six weeks to respond.

CCS assures there are no new or outstanding issues with the revised protocol by performing a review against a previous review. This review also requires ten business days, and if there are generates comments, CCS returns the protocol to the PI for further responses. If no comments result, the protocol can be sent to the FDA.

Hold Issues

The IND review may identify hold issues that must be resolved before study approval. When items are missing from a protocol submission (for example, Case Report Forms), CCS does not put the review of the protocol on hold. CCS reviews the protocol as is, notes the missing documents, and allows the PI to submit those documents with the revised protocol. CCS documents problems like this in the Medical Monitor meeting minutes.

Amendments

Prior to submission to and approval by the FDA, any change to a protocol is a revision. Once the FDA has approved a protocol, any change is an amendment.
Once the protocol is approved, the PI may request an amendment. If so, CCS will discuss the amendment with the Medical Monitor. In other cases, the Medical Monitor may request that the PI amend the protocol. In either case, CCS may perform various reviews of the amendment if needed.

Tracking Protocol Review

Typical protocol statuses recognized by CCS are In Review, Submitted (to FDA), and In Amendment (after FDA approval). PITS has a comments field in which CCS often records the date of FDA submission. That date is also recorded in other CCS Regulatory databases. CCS tracks milestones and milestone dates in various databases and links them in order to extract information. CCS would like to see any CTEP procedure manuals related to Protocol Statuses.

Phase I Trials

Sometimes Principal Investigators propose research with multiple phases. The study may contain subtasks such as a single dose phase and a multi-dose phase. Chemopreventive Clinical Services (CCS) creates a separate database record for each subtask. Recently, CCS has asked Principal Investigators to submit each subtask as a separate protocol. The database links these separate protocols under the same contract.

CCS personnel may assign an additional identifier (or ID extension) to show that each subtask is a separate protocol under the same contract. CCS uses extensions to identify different arms within a protocol.

It is common for these subtasks to occur in sequence. However, phase I protocols can have multiple agents used in the same study in parallel. CCS assigns a different extension number to each agent. Further KA is needed to identify which CCS database documents the extensions.

CCS Databases

Table 2 gives a listing of the CCS databases discussed in this report.

Type of database	Database name	Comments
Regulatory	PITRACK Principal Investigator Tracking	Principal Investigators and study institution information tracked by IND and NCI Contract Number. Data is part of Contract Status Report
	AMTRACK Amendment Tracking	Tracks IRB approval of new protocols and amendments by IND and NCI contract number. Data is part of Contract Status Report
	INDTRACK Investigational New Drug Tracking	IND status and content. IND submissions tracked by IND and serial number. Used to prepare IND Submission Tracking Report and Quarterly IND Submission Progress Reports
	AETRACK Adverse Event Tracking	Adverse Events
	SAFTRACK	Tracks and maintains archives of all submissions
Desktop	DOCTRACK	More KA needed
	CLINSUM	Detailed text fields for abstraction of site visit reports
	CPCHEMS Chemopreventive Chemical	Master list of all pre-clinical and clinical agents used in cancer prevention trials
Protocol Tracking	PITS Protocol Information Tracking System	Clinical protocols administrative info (includes accrual info) – mostly for protocol review
	CPCONTR	Pre-clinical protocols administrative info on organizations
	CPCLCON	Clinical protocols administrative info on investigators. Including scheduling site visits.
	CPCLIN	Clinical protocols test results. Provides an overview of patient accrual information.

Entries for Domain Dictionary

MPA: Multiple Project Assurances. Office of the Protection from Research Risks form used by large research hospitals, university medical schools and other organizations to protect all human subjects participating in clinical research in those organizations.

SPA: Single Project Assurance. Office of the Protection from Research Risks formal agreement negotiated when an institution doesn't have an MPA or is about to receive funding for a single research project involving human research subjects. Both MPAs and SPAs are designed to protect human subjects from unnecessary risks